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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,030	08/12/2004	Norbert E. Fusenig	0471-0286PUS1	3120

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EXAMINER	
HENRY, MICHAEL C	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
06/26/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/501,030	FUSENIG ET AL.	
	Examiner	Art Unit	
	Michael C. Henry	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *18-28, 30* is/are allowed.

6)☒ Claim(s) *1-17 and 29* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The following office action is a responsive to the Amendment filed, 03/19/07.

The amendment filed 03/19/07 affects the application, 10/501,030 as follows:

1. Claim 10 has been amended.

2. The responsive to applicants' arguments is contained herein below.

Claims 10-30 are pending in the application

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 10 is rejected under 35 U.S.C. 102(b) as being anticipated by Sakurai et al. (JP 61000017).

In claim 10, applicant claims "A method for the treatment and care of primary and secondary tumors by inhibiting angiogenesis which comprises applying at the tumor site a biomaterial comprised of: (a) a benzyl ester of hyaluronic acid, or (b) a cross-linked hyaluronic acid having carboxy groups cross-linked to the-hydroxyl groups of the same hyaluronic acid molecule or a different hyaluronic acid molecule, wherein said biomaterial inhibits angiogenic processes related to vascularization." Sakurai et al. disclose applicant's method for the treatment of tumors by inhibiting or preventing the metastasis of the tumor which comprises applying (injecting) at the tumor site a biomaterial comprised of a cross-linked hyaluronic acid derivative (see abstract). It should be noted that the examiner considers the inhibition of angiogenesis the

mechanism by which said tumor treatment occurs. Furthermore, it should also be noted that since Sakurai et al. applies the same biomaterial or composition to the same tumor site as applicant it should inherently have the same effect of inhibiting angiogenesis as applicant's composition. In addition, it is well known in the art that angiogenesis is significant in the development of metastasis and that the inhibition of angiogenesis inhibits metastasis.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-17, 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakurai et al. (JP 61000017).

In claim 10, applicant claims "A method for the treatment and care of primary and secondary tumors by inhibiting angiogenesis which comprises applying at the tumor site a biomaterial comprised of a benzyl ester of hyaluronic acid or a cross-linked derivative of hyaluronic acid wherein the carboxy groups of hyaluronic acid are cross-linked to the hydroxyl group of the same or different hyaluronic acid molecule; wherein said biomaterial inhibits angiogenic processes related to vascularization." Claims 11, 15-17, 29 are drawn to said method wherein the hyaluronic acid is in association with other natural, synthetic and/or semisynthetic biopolymers, pharmacologically active substance, specific pharmacological active substance, specific forms of the biomaterial and specific form of application to tumor site.

Sakurai et al. disclose applicant's method for the treatment of tumors by inhibiting or preventing the metastasis of the tumor which comprises applying at the tumor site a biomaterial or composition comprised of a cross-linked hyaluronic acid derivative (see abstract). It should be noted that the examiner considers the inhibition of angiogenesis the mechanism by which said tumor treatment occurs. Furthermore, it should also be noted that since Sakurai et al. applies the same biomaterial or composition to the same tumor site as applicant it should also inherently have the same effect of inhibiting angiogenesis. In addition, it is well known in the art that angiogenesis is significant in the development of metastasis and that the inhibition of angiogenesis inhibits metastasis. Furthermore, Sakurai et al. disclose that their cross-linked hyaluronic acid derivative composition has analgesic and tissue restoration effect (see abstract).

The difference between applicant's claimed method and the method disclosed by Sakurai et al. is that Sakurai et al. do not disclose the use of pharmacologically active substance (such as anti-tumor compounds) in association with their composition. However, it is obvious to prepare a composition comprising the combination of compounds that have the same utility to treat the same condition or disease.

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made, in view of Sakurai et al., to have used the method of Sakurai e al. to treat tumors with a composition comprising a combination of a crosslinked hyaluronic acid derivative and a pharmaceutically active substance such as the anti-tumor substance, cis-platinum, since the combination of compounds that are used to treat the same diseases are well known in the art. More specifically, it is obvious to combine individual compositions taught to have the same

utility to form a new composition for the very same purpose. In re Kerkhoven, 626 F.2d 846, 205 U.S.P.Q. 1069 (C.C.P.A. 1980).

One having ordinary skill in the art would have been motivated in view of Sakurai et al., to have used the method of Sakurai e al. to treat tumors with a composition comprising a combination of a crosslinked hyaluronic acid derivative and a pharmaceutically active substance such as the anti-tumor substance, cis-platinums, because a skilled artisan would reasonably be expected to prepare a composition comprising a combination of the compounds that are taught to have the same utility, to treat tumors based on type and/or severity of the tumor condition or disease. It should be noted that the use of crosslinked hyaluronic acid composition in specific forms or formulations and with other biopolymers (such as for the administration or application of medicaments or active ingredient is common in the art and depends on factors such as the type and condition of tumor treated.

Allowable Subject Matter

The following is an examiner's statement of reasons for allowance: The examiner has found claims 18-28, 30 to be unobvious over the prior art of record and therefore to be allowable over the prior art of record of record. The present invention relates to a method for the treatment and care of primary and secondary tumors by inhibiting angiogenesis which comprises applying at the tumor site a biomaterial comprised of a benzyl ester of hyaluronic acid wherein said hyaluronic acid is at least specific % benzyl esterified, and wherein said biomaterial inhibits angiogenic processes related to vascularization. The very relevant prior art document Sakurai et al. (JP 61000017) does not disclose or suggest the method of treating tumors with benzyl ester of

hyaluronic acid much less the use of hyaluronic acid that is benzyl esterified at the claimed % to treat said tumors.

Response to Amendment

Applicant's arguments with respect to claims 10-17, 29 have been considered but are not found convincing.

The applicant argues that it is well known that the cross-linking between hyaluronic acid and epoxy compounds disclosed by Sakurai et al. occurs only through ether bond formation; whereas the cross-linking among hyaluronic acid molecules presently claimed occurs through ester bond formation. It follows that Sakurai et al. fails to teach the presently claimed invention, and the anticipation rejection is improper. On the contrary, Sakurai et al. use multifunctional epoxy compounds, bisepoxy compound and halomethyloxirane such as epichlorohydrin. Such multifunctional epoxy compounds such as epichlorohydrin gives cross-linked esters of hyaluronic acid (for example, see US 4,957,744, col. 1, line 45 to col. 2, line 4; see also US 4,716,224, abstract and example 4, cols. 7-8). Thus, the cross-linking among hyaluronic acid molecules in Sakurai et al. does occurs through ester bond formation as well as ether. That is, epichlorohydrin is a polyfunctional epoxy compound that can react with both carboxyl and alcohol groups of hyaluronic acid.

The applicant argues that Sakurai et al. entirely fails to even mention the use of Applicants' claimed compounds in the context of treating and caring for tumors by inhibiting the angiogenic process, as claimed by Applicants. Sakurai et al. only discloses that its biomaterials are useful in cosmetics, in treating retinal detachments, in treating diabetic retinopathy and in healing diseased tissues (column 4, lines 1-60). For this reason as well, Sakurai et al. fails to

anticipate the presently claimed invention. On the contrary, Sakurai et al. disclose a method for the treatment of tumors by inhibiting or preventing the metastasis of the tumor which comprises applying (injecting) at the tumor site a biomaterial comprised of a cross-linked hyaluronic acid derivative (see abstract; see also STN of JP 61000017)).

The applicant argues that Sakurai et al. teaches away from the presently claimed invention. In particular, Applicants submit that the epoxide derivatives disclosed by Sakurai: epichlorohydrin, epibromohydrin, and bisphenol A diglycidyl ethers are generally toxic compounds. Moreover, epichlorohydrin causes cancer (see for example the enclosed Haz-Map literature). It follows that Sakurai et al. teaches away from the presently claimed invention of a method for treatment of primary and secondary tumors. However, it is hyaluronic acid, and not epichlorohydrin, that is used to treat the tumor. Epichlorohydrin is only used as the cross-linking agent. Furthermore, Sakurai et al. disclose that the cross-linked hyaluronic acid prevented metastasis of the tumor and does not disclose any toxic effect caused by said cross-linked hyaluronic acid.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Henry whose telephone number is 571-272-0652. The examiner can normally be reached on 8.30am-5pm; Mon-Fri. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael C. Henry

6/15/07

Shaojia Anna Jiang, Ph.D.
Supervisory Patent Examiner
Art Unit 1623

June 14, 2007.